

Spring 3-16-2011

Aortic Root Replacement: A Comparison of Valve-Sparing Procedures With Mechanical Valve Replacement in Patients With Marfan Syndrome

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Abstract

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Methods: An extensive review of the literature was conducted using Medline-Ovid, PubMed, and Cinhal. Three articles that met the inclusion criteria were included in the review.

Results: Similar intraoperative and early mortality rates were demonstrated between aortic root replacement with AVR and AVS. Two studies showed increased late morbidity of thromboembolic events associated with AVR compared to AVS. Follow-up times between the two groups in each study differed drastically, making it difficult to draw final conclusions regarding long-term outcomes.

Conclusions: Although aortic root replacement with either AVR or AVS provides a low risk of early mortality, there are insufficient long-term data on late mortality that support recommending valve-sparing (AVS) procedures over valve-replacing (AVR) procedures at this time. After applying the GRADE system to the review, the overall quality of the evidence was determined to be low.

Keywords: Marfan syndrome, valve-sparing, heart valve prosthesis

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Subject Categories

Medicine and Health Sciences

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Aortic Root Replacement: A Comparison of Valve-Sparing Procedures With
Mechanical Valve Replacement in Patients With Marfan Syndrome

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A course paper presented to the College of Health Professions
in partial fulfillment of the requirements of the degree of
Master of Science

Pacific University School of Physician Assistant Studies

March 16, 2011

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Biography

Gabriel Reed Smith was born in the great State of Texas, though he has lived across the U.S. including Miami, Iowa City, Santa Fe, and most recently Portland. He has a beautiful wife, but no kids. He very much looks forward to becoming gainfully employed.

ABSTRACT

Background: Historically, surgical replacement of the aortic root in Marfan syndrome patients involved replacing the native valve with a mechanical valve resulting in the need for life-long anticoagulation. Recently, surgeons have developed procedures that spare, rather than replace the aortic valve during aortic root replacement. The goal of this systematic review is to compare valve-sparing aortic root replacement with traditional aortic root replacement with mechanical valves, and evaluate the evidence using the GRADE system.

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TABLE OF CONTENTS

INTRODUCTION	6
METHOD	8
RESULTS	10
I. Aortic Root Replacement in 372 Marfan Patients: Evolution of Operative Repair Over 30 Years	
a. Patient characteristics	
b. Operative technique	
c. Intraoperative & early results	
d. Late Results	
II. Comparison of Aortic Valve-sparing Reimplantation Versus Composite Grafting	
a. Patient characteristics	
b. Operative techniques	
c. Early results	
d. Late results	
III. Aortic Valve Operative Outcomes in Marfan Patients	
a. Patient characteristics	
b. Operative techniques & data	
c. Early morbidity & mortality	
DISCUSSION.....	21
I. GRADE	
a. Study limitations	
b. Early morbidity & mortality in AVR and AVS	
c. Late morbidity in AVR and AVS	
d. Late mortality in AVR and AVS	
CONCLUSION.....	26
REFERENCES	27
APPENDIXES.....	29
A. GRADE Table	
B. List of Abbreviations	

INTRODUCTION

Background

Prior to advances in medical technology and surgical techniques in the mid-20th century, men and women with the inherited connective tissue disorder first described in 1896 as Marfan syndrome (MFS) were at high risk of premature mortality secondary to cardiovascular complications such as aortic aneurysm, aortic regurgitation, and aortic dissection (De Paepe, Devereux, Dietz, Hennekam and Pyeritz, 1996). In general, life expectancy for these patients was between twenty and thirty years (Murdoch, Walker, Halpern, Kuzma, and McKusick, 1972). However, as cardiothoracic surgery around the globe became more advanced and surgeons began experimenting with methods that focused on replacing aortic roots in MFS patients with composite grafts and mechanical valves, life expectancies improved (Cameron et al., 2009).

In 1968, the Bentall procedure was published in the literature (Bentall and DeBono, 1968). First performed by Dr. Hugh Bentall and Anthony De Bono at London Hammersmith Hospital, the surgery involved replacing the proximal portion of the ascending aorta with a Teflon graft, and substituting a durable, mechanical Starr aortic valve in place of the patient's native aortic valve (Bentall and DeBono, 1968). This procedure, hereafter referred to as AVR, provided a number of advantages for patients with Marfan syndrome. For instance, patients whose aortic roots were already dangerously dilated, or who had pre-existing aortic aneurysms or dissections could now be surgically treated with favorable long-term survival rates (Cameron et al., 2009). However, having an implanted mechanical valve meant mandatory long-term anticoagulation to prevent fatal thromboembolic events. As such, the use of anticoagulants such as warfarin sodium in MFS patients carries a risk of life-

threatening complications from bleeding (Horstkotte, Shulte, Biercks, and Strauter, 1993). Although the Bentall procedure has been the “gold standard” for aortic root replacement since the late 1960s, newer procedures have emerged that rely on methods of salvaging and repairing native aortic valves in patients who need surgical intervention on their aortic roots (Gott et al., 1999).

Birks et al. (1998) found that aortic valve-sparing root replacement (AVS) emerged in the later half of the 20th century as a way to repair aortic aneurysms and dilated aortic roots in patients with MFS without having to utilize mechanical or bioprosthetic valves. Surgeons began to experiment with methods of preserving the native aortic valves in MFS patients hoping this would provide an effective alternative—especially for children, young adults, and women desiring to become pregnant—to traditional non-valve sparing techniques that required lifelong anticoagulation. David and Feindel (1992) showed that early results were promising. As more young patients with MFS began to undergo prophylactic aortic root replacement to prevent future complications from aortic aneurysm and dissection, AVS procedures began to gain ground among cardiothoracic surgery programs. Although the Bentall procedure is still the preferred method for definitive root replacement in MFS patients due to its durability and reproducible results, AVS root replacement appears to be a good alternative for non-emergent aortic root replacement when the patient’s aortic valve is salvageable (Cameron et al., 2009). Still, because it is a “newer” procedure and has not been widely adopted as a standard method for aortic root replacement, the data are somewhat limited when compared to traditional AVR.

Purpose of the Study

The purpose of this study is to review the literature on aortic root replacement with AVR versus AVS in Marfan syndrome patients, and to explore differences in early and late morbidity and mortality. Ultimately, by utilizing a standardized GRADE (Grading of Recommendations Assessment, Development and Education) system, the studies included in this review will be critically appraised and “graded” according to this system. This GRADE system is an internationally recognized method whose purpose is to rank the quality of evidence according to certain characteristics and variables. For instance, randomized clinical control trials are considered to be of the highest quality evidence. Still, the quality of evidence found in randomized trials can be lowered due to study limitations, inconsistency of results, indirect evidence, imprecise results, and bias. On the other hand, cohort and case-control studies are considered to be low quality evidence. However, a low quality study may be graded upwards if the treatment effect is large, or if there is evidence of a dose-response relationship. In this review, after reviewing the results, the treatment effect, and any study limitations, a final ranking will be given to the evidence as a whole, and will result in a high, moderate, low, or very low grade.

METHOD

A systematic review of the literature was conducted using the following search vehicles: Medline-Ovid, PubMed, and Cinhal. Studies were sought comparing outcomes between aortic root replacement with valve-sparing procedures (AVS) and aortic root replacement with mechanical valve replacement (AVR). These databases were accessed through the Pacific University Library system. The search was limited to studies published since 2001, written in the English language, involving human

subjects, and included in Core Clinical Journals. Several defined key words or phrases including “Marfan Syndrome,” “valve-sparing,” and “heart valve prosthesis” yielded a total of 19 articles. After applying the inclusion and exclusion criteria listed below, three articles were included for review.

Inclusion Criteria

Articles that directly addressed outcomes between aortic valve-sparing procedures and composite grafting with mechanical valve replacement were included. Articles whose study populations consisted of pediatric and adult patients were included. Since valve-sparing procedures are a relatively recent phenomenon with the newest AVS techniques becoming more globally disseminated within the last ten years, only studies published after 2001 were included.

Exclusion Criteria

Duplicate articles, as well as editorial articles, case studies, and meta-analyses were not included for purposes of this systematic review. A large number of studies whose abstracts were reviewed compared outcomes between different types of valve-sparing procedures. As these studies did not specifically address the clinical question, they were excluded. Studies whose primary participants did not have the Marfan syndrome were also not included.

Two relevant studies (Gott et al., 2002 and Patel et al., 2008) discovered during the literature search were versions of a final study published in 2009 (Cameron et al., 2009). For purposes of clarity, and so as to not re-synthesize similar data three separate times, both earlier versions were excluded.

RESULTS

Three studies were chosen for review. They consisted of two retrospective cohort studies and one prospective cohort study. There were no randomized control trials that met the inclusion and exclusion criteria. In brief, a total of 642 patients enrolled in these three studies and previously diagnosed with Marfan syndrome underwent aortic root replacement between September 1976 and January 2008. Three hundred eighty-nine patients received AVR with a composite graft and mechanical valve, 235 received AVS, 16 had AVR with homografts, and 2 patients received AVR with porcine xenografts. The two retrospective studies were performed at the world-renowned medical institutions Johns Hopkins Medical Center in Baltimore, Maryland and Hannover Medical School in Hannover, Germany. The prospective cohort study was implemented by a consortium of researchers who designed an international registry study from 18 sites in Europe and North and South America.

Aortic Root Replacement in 372 Marfan Patients: Evolution of Operative Repair Over 30 Years

In this retrospective cohort study by Cameron et al. (2009) spanning three decades, 372 Marfan syndrome patients who underwent aortic root replacement with AVR versus AVS were analyzed for outcomes including early and late morbidity and mortality, as well as freedom from thromboembolism, and reoperation rates. Two hundred sixty-nine patients received composite graft repair (AVR, aka Bentall procedure), 85 patients underwent aortic root replacement with AVS, 16 received a homograft, and two had porcine xenografts. Participants underwent surgical procedures and subsequent follow-up between September 1976 and September 2006. All patients were pooled from a single collegiate institution: Johns Hopkins Medical Center. Data regarding study participants was generated from clinical records, and

follow-up was conducted by directly contacting the patients and their primary care providers.

Patient characteristics

Of the patients 265 patients were male (71%), and 107 were female (29%). Patient age was separated into four groups. Twenty pediatric patients (< 18yr) had AVR, and 19 had AVS. Sixty-six (66) patients between the ages of 18-27 had AVR, and 18 had AVS. Eighty-nine (89) patients between the ages of 28-37 had AVR, and 21 received AVS. Ninety-four (94) patients older than 38 (> 38yr) had AVR, and 27 had AVS. Mean age was 32.9 years, with an extremely wide range (1.5 to 73 years). In the AVR group, a total of 59 patients had aortic dissections at the time of operation; 27 of those were classified as acute (< 14 days old), and 34 were chronic (> 14 days old). There were no aortic dissections noted in the AVS group. A total of 327 patients underwent elective surgery, whereas 45 patients underwent urgent or emergent surgery.

Operative technique

Between 1976 and 2000, 85% of all patients who underwent surgery had AVR consisting of a Bentall composite graft with mechanical valve replacement. Between 1998 and 2006, a total of 61% of all patients undergoing surgery had AVS. All 85 patients who underwent AVS received one of two variations in valve-sparing procedures. Forty patients received a David II remodeling procedure, and one patient received a David I reimplantation. A total of 44 patients received a David reimplantation technique with Valsalva graft. From May 2002 until the conclusion of the study, this

modified reimplantation method with aforementioned Valsalva graft was the preferred technique utilized by surgeons.

Intraoperative & early results

Of the patients who underwent elective surgery in either group (n=327), there were no operative deaths, and there were no mortalities noted within 30 days of surgery. Of the 45 patients who underwent emergent surgery, two deaths occurred within 30 days of the operation. The two intraoperative deaths resulted from a ruptured aorta with subsequent pericardial tamponade. Within the group of 45 patients who underwent emergent surgery, 35 patients had either acute or chronic aortic dissection, and 10 patients had imminent aortic rupture, or impaired cardiac output resulting from a dysfunctional left ventricle.

Late results

Of the 370 patients who survived beyond thirty days post-operatively, 74 deaths had occurred at the time of the study's conclusion. Ten patients died from complications due to dissection or rupture of the residual aorta. Nine patients died from complications of heart arrhythmia, and three patients died of prosthetic heart-valve endocarditis. In 26 cases, cause of death was unknown. The remaining deaths were attributed to a wide variety of etiologies including congestive heart failure, intracerebral hemorrhage, sepsis, multi-organ failure, cancer, drug overdose, motor vehicle accident, peritonitis, and respiratory failure. Of the 74 deaths, 70 patients had received AVR with a Bentall composite graft, 2 patients had AVS, and 2 had a homograft. Of the 2 mortalities in the AVS cohort, one died secondary to complications of a thoracoabdominal aortic aneurysm repair 9 years after receiving AVS, and one died 10

years after AVS from biventricular failure while awaiting heart transplantation. Of the 44 patients with AVS who received the newer Valsalva graft, there were no late deaths by the conclusion of the study.

Late morbidity outcomes including thromboembolism and reoperation rates were also analyzed between patients receiving AVR and AVS. Of the 370 patients who survived 30 days beyond their operation, 19 patients suffered from thromboembolism. All 19 patients belonged to the AVR group. Forty-nine patients (13.2%) of the 370 original survivors underwent late aortic surgeries (classified as the aortic arch and distal to this) for worsening aneurysm or dissection of the residual aorta. In total, freedom from reoperation at five, 10, 15, and 20 years was 95.6%, 88.8%, 82.2%, and 72.1%, respectively. The researchers also found that having a pre-existing aortic dissection prior to the operation played a major role in long-term survival rate and freedom from reoperation among MFS patients. For patients who presented initially with aortic dissection, freedom from reoperation at 10 years was 67%, and at 20 years 43%. For those patients without initial dissection, freedom from reoperation at 10 years was 92%, and at 20 years was 77%.

The researchers utilized several variables to determine risk factors that might contribute to early and late morbidity and mortality, and analyzed the variables using univariate and multivariate statistical models. These risk factors included patient age, concomitant mitral valve surgery, preoperative aortic dissection, NYHA class III/IV heart failure status, urgent surgery, and male gender. Independent mortality predictors as shown using univariate analysis were the presence of preoperative aortic dissection (Hazard Ratio 2.33, $p=0.002$), poor NYHA heart failure status of grade III/IV (Hazard

Ratio 2.24, $p=0.001$), and need for emergent surgery (Hazard Ratio 2.51, $p=0.003$).

However, using multivariate analyses the authors showed that only concomitant mitral valve surgery (Hazard Ratio 1.85, $p=0.039$) and preoperative aortic dissection (Hazard Ratio 1.90, $p=0.054$) were predictors of early and late mortality that were statistically significant.

Cameron et al. (2009) concluded that patients with the Marfan syndrome benefit from prophylactic surgical intervention and replacement of the aortic root to prevent late complications from aneurysm and dissection, be it by AVR or AVS. The study demonstrated that there is a lower risk of thromboembolism in valve-sparing procedures. The initial desire to avoid life-long anticoagulation was also satisfied. Still, because of lack of long-term follow-up in the AVS group, the authors determined it is yet unknown how durable AVS is compared to traditional AVR regarding late mortality and freedom from reoperation. The authors concluded that not all Marfan patients are candidates for AVS, which largely depends on whether or not their aortic leaflets are healthy enough to support AVS in the long-term. This is largely based on physician opinion and preference at the time of surgery.

Comparison of Aortic Valve-sparing Reimplantation Versus Composite Grafting

Karck et al. (2004) conducted a retrospective cohort study involving 132 patients previously diagnosed with Marfan syndrome who underwent aortic root surgeries at Hannover Medical School in Hannover, Germany between March 1979 and April 2002. Seventy-four patients with MFS underwent AVR, and 45 patients received AVS. Together, these two cohorts consisted of a total of 119 patients. The remaining 13 patients who underwent aortic root replacement during the study period received

certain procedures not related to either AVR with mechanical aortic valve or AVS, and were therefore not included in final analysis. Follow-up was conducted on an annual basis. The mean follow-up in patients who had AVR was 114 ± 63 months (range 2-249), compared to 30 ± 27 months (range 1-95) for AVS patients. The authors indicate that no patients were lost to follow-up. As part of follow-up, serial echocardiography was completed in patients who underwent AVS, and patients who had aortic dissection and sub-critical dilatation of the aorta underwent routine computed tomography as a method to monitor for late complications.

Patient characteristics

At study conclusion, a total of 74 patients underwent AVR. The mean age in the AVR group was 35 ± 11 years. Forty-five patients underwent AVS with a mean age of 28 ± 12 years. A total of 29 (64%) males and 16 (36%) females received AVS. Forty-nine males (66%) and 25 (34%) females underwent AVR. In the AVS cohort, three (7%) patients had acute aortic dissections, and one (2%) had a chronic dissection. Among the AVR group, 17 (23%) patients had acute dissections, and 22 (30%) had chronic dissections. Nine (12%) patients in the AVR cohort were noted to have had previous cardiac surgery, compared to zero in the AVS group.

Operative techniques

Of the 45 patients who received AVS, each underwent a David reimplantation operation. Extracorporeal circulation time was longer in the AVS group: 162 ± 34 minutes, compared to 124 ± 45 minutes in the AVR group with a statistically significant p value ($p=0.0001$). There were additional procedures completed in the AVS patients that were statistically significant. Eight (18%) AVS patients had concomitant mitral

valve repair, compared to zero in the AVR group ($p = <0.0001$). Ninety-nine patients underwent elective operations, compared to 20 patients who underwent emergent surgeries for acute aortic dissection.

Early results

Early mortality results showed five (6.8%) patients in the AVR group died before hospital discharge. Of these five patients, three patients died from complications associated with mediastinal bleeding, one patient died from sepsis, and one died from stroke. There were no early mortalities in the AVS group. Eight patients in the AVR group and two patients in the AVS group needed early reoperation to determine a source of mediastinal hemorrhage. The length of hospital stay was slightly longer in the AVR group 20 ± 18 days, and 15 ± 9 days in the AVS group. The researchers reported no perioperative incidence of cerebrovascular accident, myocardial infarction, or infection in the AVS cohort. Two patients in the AVR group had non-mortal strokes, two patients sustained neurological deficits secondary to cerebral ischemia, and one patient had a transient ischemic attack. In the early follow-up period, 12 patients in the AVR group sustained hemorrhages unrelated to surgery. Three patients developed cerebral hemorrhage, three had retinal bleeding, three had gastrointestinal bleeding, and three more developed severe epistaxis. There was no hemorrhage reported in the AVS cohort during early follow-up.

Late results

Late survival rates were measured at one year, five years, and 10 years in the AVR group and compared to survival rates in the AVS group. At one year in the AVR cohort, survival was $97 \pm 2\%$, at 5 years $89 \pm 4\%$, and at 10 years $76 \pm 4\%$. Duration of

survival for the AVS cohort measured 100% at one year, and $96 \pm 4\%$ at five years, though the comparison was not statistically significant ($p=0.54$). There were no data in the AVS group regarding survival that extended to 10 years or beyond. Rates of reoperation were also measured during late follow-up in both cohorts. Aortic valve reoperation in the AVS group occurred in four patients (9%) due to complications with aortic valve incompetence, aortic insufficiency, and subsequent distal aortic replacement. All four patients ultimately received AVR with mechanical valve prosthesis following reoperation. A total of seven patients (9%) in the AVR cohort underwent subsequent reoperation. Six of these patients required reoperations on the composite graft placed at the initial operation. One patient received a heart transplant after worsening cardiomyopathy following AVR. Two of the seven patients died during the early postoperative period. Freedom from reoperation was calculated in both groups and again measured at one, five, and 10 years following initial operation. In the AVR cohort, freedom from reoperation was $97 \pm 2\%$ at 1 year, $92 \pm 3\%$ at 5 years, and $92 \pm 3\%$ at 10 years. In the AVS group, freedom from reoperation was $95 \pm 4\%$ at one year, and $84 \pm 8\%$ at five years. There was no statistical significance between the differences ($p=0.31$).

Karck et al. (2009) concluded that in-hospital mortality, survival rate at five years, and incidence of reoperation between AVR and AVS patients with MFS were similar. The authors determined that despite the fact that long-term follow-up is needed to elucidate differences in overall mortality, AVS root replacement surgeries appear to be effective in the short-term, and prevent patients from having to sustain lifelong anticoagulation regimens.

Aortic Valve Operative Outcomes in Marfan Patients

Volguina et al. (2009) analyzed perioperative and early 30-day outcomes in 151 MFS patients who underwent either AVR or AVS in this prospective cohort study. Eighteen centers in Europe, and North and South America consecutively enrolled patients who met criteria for Marfan syndrome between March 2005 and January 2008. Criteria for enrollment included patient consent, need for aortic root surgery, availability for prospective follow-up, and previous diagnosis of Marfan syndrome. Participating study sites gathered patient data and preoperative status, type and method of operation, and post-operative status that was submitted to a central Data Coordination Center (DCC) for pooled analysis. To ensure quality control, the DCC performed annual inspections of participating facilities and verified protocol compliance, and appropriate documentation. The primary outcome the authors were looking for was incidence of any and all valve-related complications within 30 days of surgery. The researchers set a target sample size of 250 patients that would provide 80% power ($\alpha = 0.05$) to distinguish a 1.85-fold increase in relative risk of valve-related problems between both AVR and AVS cohorts. This statistical measure was determined by an estimated event rate of approximately 20%.

Patient characteristics

Baseline patient variables including aortic dimensions, preexisting acute and chronic dissections, ejection fraction, and prevalence of diabetes, hyperlipidemia, hypertension, coronary artery disease, mitral valve disease and coagulopathies were similar between groups. Still, patient characteristics differed in a number of significant ways. Patient age in the AVR group was 39 ± 13 years, compared to 31 ± 12 years (p

<0.01) in the AVS group. Significantly more patients in the AVR group had severe (9/45, 20%) aortic regurgitation compared to AVS where prevalence of severe aortic regurgitation was (5/99, 5%). Also, a disproportionate number of patients in the AVR group had previously undergone cardiovascular surgery (6, 13%) compared to four patients (4%) in AVS cohort.

Operative techniques & data

Urgent and emergent surgeries were more likely in the AVR group (n=12, 24%) than 6 (6%) in the AVS group. Perfusion techniques were similar between both groups. Median cardiopulmonary bypass time differed between groups with median time for AVR 148 minutes (range 107-199) and 191 minutes (range 157-271) for AVS (p <0.01). Median aortic cross-clamp times were also different. In the AVR group, median cross clamp time was 114 minutes (range 76-166) and 150 (120-225) in the AVS group (p <0.01). The researchers determined from questionnaire data completed by the participating surgeons that final decisions to perform AVR or AVS were made intraoperatively almost half of the time (43%).

Early morbidity and mortality

Early results showed there were no 30-day, intraoperative, or in-hospital mortalities in either the AVR or AVS group. Valve-related problems occurred in both groups during the 30-day postoperative period and were similar 2/46 (4%) in the AVR group, versus 3/105 (3%) in the AVS group. The authors showed that this was not statistically significant (p=0.6). Complications including embolism, acute renal failure, mediastinal bleeding, and multiple organ failure were similar between groups. Cardiac complications such as arrhythmia, pericardial effusions and cardiac failure were also

similar. Although total time spent recovering in the ICU was greater in the AVR group, it was not statistically significant ($p=0.5$).

Volguina et al. (2009) concluded that root replacement in MFS patients with AVR or AVS had low mortality rates at least in the short-term post-operative period. Also, they demonstrated through statistical analysis that the type of root replacement received (AVR vs AVS) was not a predictor of early valve-related complications. The researchers concluded aortic root replacement with AVS was the most common procedure performed in clinical practice.

DISCUSSION

GRADE

According to the aforementioned GRADE system, the quality of the evidence is defined in the following manner:

High quality— Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality— Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality— Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality— Any estimate of effect is very uncertain. (Guyatt et al., 2008, p. 926)

Since all three studies included in this systematic review were cohort studies, by virtue of their design (according to GRADE) they were categorized as low-quality evidence.

Unfortunately, each study was unable to increase their grade due to the specific limitations that are discussed in detail below. Therefore, the overall GRADE of the evidence is deemed low quality (Appendix A, Table 1).

Study limitations

There are multiple reasons why surgical interventions are difficult to compare head-to-head in order to determine superiority by utilizing a randomized control methodology. For instance, urgency of surgery, anatomical differences between patients, certain ethical considerations, and variations in surgical training and operative technique are but a few variables that prevent randomization. Despite this, even small, non-randomized studies can be elucidating to some degree and if used in the appropriate context can even mold clinical decisions regarding patient care. In this systematic review, all three studies included were non-randomized cohort studies and are therefore designated low quality due to their design. As such, one of the most significant limitations of these studies was that the decision to perform either aortic root replacement with AVR or AVS was made intraoperatively by the operating surgeon at least half the time, suggesting that bias could have been systematically introduced. Additionally, In both Cameron et al. (2009) and Karck et al. (2004), the long duration of these retrospective cohort studies of 30 and 23 years, respectively, meant that operative techniques were constantly evolving and then being introduced to the study populations in an ad-hoc, non-standardized way. Therefore, follow-up times were different between groups and subgroups and potentially make the final results less significant. It is important to mention that, as valve-sparing reimplantation techniques changed during the study's timeframes, these techniques inevitably replaced older methods, thus altering the composition of the AVS study groups and their follow-up times to an even greater degree. Yet another potential limitation is the fact that patient characteristics between the AVR and AVS cohorts in each study were different in several major regards, thus potentially marring statistical significance of outcomes

between groups. This fact, and the fairly small study populations potentially made the studies more limited in significance.

Early mortality & morbidity in AVR and AVS

All three studies showed similar rates of intraoperative mortality between patients who underwent AVR and AVS. In Cameron et al. (2009), there were no intraoperative mortalities in patients undergoing elective surgery, and only two deaths in patients who underwent emergent surgeries, both of whom ultimately received AVR procedures. Karck et al. (2004) showed that five patients who received AVR died in the hospital compared to none in the AVS cohort. Volguina et al. (2009) had no intraoperative mortalities in either group. It is interesting that despite longer cross-clamp times and the increased technical demands of AVS surgery, it demonstrated a low risk of intraoperative mortality in all three studies. In other words, it would appear that all three studies showed that although there is a risk of intraoperative mortality associated with AVR and AVS procedures, in younger, healthier MFS patients undergoing elective root replacement surgeries, the risk appears to be negligible. Still, this fact may become less significant after considering the patients who died intraoperatively were older, had greater need for urgent/emergent surgeries, and tended to have more acute and chronic aortic dissections than their counterparts who underwent elective aortic root replacement with AVS.

One study showed there was a higher incidence of early reoperation in the AVR group secondary to surgical bleeding complications when compared to the AVS group, although this was not highlighted in the other studies (Karck et al., 2004). Volguina et al. (2009) demonstrated similar early morbidity outcomes across the board when

comparing AVR to AVS. Cameron et al. (2009) did not specifically address early morbidity and focused instead, on early mortality.

Late morbidity in AVR and AVS

Only two studies (Cameron et al., 2009, & Karck et al., 2004) had long enough follow-up periods to allow them to adequately address late morbidity between the AVR and AVS groups. Comparatively, both studies showed similar rates of reoperation between AVR and AVS cohorts, though Karck et al. (2004) demonstrated that at the 5-year follow-up period freedom from reoperation in the AVS group was lower ($84\% \pm 8\%$) compared to the AVR group ($92\% \pm 3\%$). However, the results do not appear to be statistically significant with a p-value shown by the authors to be ($p=0.31$). Specifically, the reoperations in the AVS group in the Karck et al. (2004) study were attributed to early valve failure secondary to “inadequate technique at the primary repair,” and the patients ultimately required mechanical valve prostheses with subsequent lifelong anticoagulation with warfarin. On the other hand, the majority of patients in the AVR group in the Karck et al. (2004) study who underwent reoperation, did so due to complications of their composite aortic grafts.

Although thromboembolic events in the Cameron et al. (2009) study numbered fairly low within the AVR group, it was the most ubiquitous complication when looking at late morbidity among this group. A total of 19 patients suffered from thromboembolic events in the AVR cohort, though freedom from this risk at 20 years was quite good at 91.5%. Similarly, Karck et al. (2004) discovered that a total of 17 patients in the AVR group suffered either bleeding episodes or thromboembolic events during late follow-up. Neither study specifically addressed whether patients suffering from

thromboembolic events or late bleeding complications in the AVR groups did so secondary to problematic anticoagulant use such as subtherapeutic INR, non-compliance with medications, or bleeding attributed to other causes. In fact, how patients were medically managed regarding the use of anticoagulants after their surgeries was never touched upon in any of the studies.

Late mortality in AVR and AVS

The Cameron et al. (2009) and Karck et al. (2004) studies addressed late mortality, though follow-up times were much longer in the AVR group compared to those in the AVS group. Cameron et al. (2009) noted 74 total deaths in those who survived to discharge. Seventy of those patients had aortic root replacement with AVR. The most common causes of death in this group were attributed to residual aortic dissection or rupture, and cardiac arrhythmia. Two late deaths were attributed to aortic root replacement with AVS. Interestingly, of the total 85 patients who underwent AVS, the two deaths were in the subgroup that received the earlier “remodeling” AVS technique. There were no deaths in the “reimplantation” subgroup by the study’s conclusion. However, because the exact amount of follow-up time was not specifically indicated between the groups and subgroups in the Cameron et al. (2009) study, it is difficult to find statistical significance in the data. Late mortality and survival rates were also similar in the Karck et al. (2009) study. Although this study, too, had varied amounts of follow-up time between AVR and AVS groups, at five years survival was $96\% \pm 4\%$ for AVR, and $89\% \pm 4\%$, though this was not shown to be statistically significant ($p=0.54$). Indeed, at 15 years postoperatively, survival rates in the AVR

group approximated survival rates in the AVS group measured at five years. Longer follow-up in the AVS group will be needed to elucidate further differences in outcome.

CONCLUSION

Prophylactic aortic root replacement should be offered as an elective surgery to MFS patients with dilated aortic roots who may be at risk for catastrophic aortic dissection or aortic rupture. Although aortic root replacement with either AVR or AVS appears to provide a low risk of intraoperative and early mortality, there are insufficient long-term data that support recommending valve-sparing (AVS) procedures over valve-replacing (AVR) procedures. Because aortic root replacement with AVR is the “gold standard” with proven durability despite the concomitant need for life-long anticoagulation, it should continue to be the standard of care for aortic root replacement in MFS patients. More long-term follow-up regarding late mortality in MFS patients who have received aortic root replacement with AVS is needed before there is a paradigm shift.

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APPENDIX A.

Comparison	Outcome	Quantity and type of evidence	Findings	Starting grade	Decrease GRADE					Increase GRADE			Grade of Evidence for Outcome	Overall GRADE of Evidence
					Study Quality	Consistency	Directness	Precision	Publication Bias	Large Magnitude	Dose-Response	Confounders		
Aortic root replacement with AVR vs. Aortic root replacement with AVS	Intraoperative mortality	3 cohort studies	Low risk. Similar findings b/w AVR AVS	Low	0	0	0	0	0	0	0	0	Low	Low
	Early morbidity, e.g. Risk of thrombo-Embolism, reoperation rates, etc.	3 cohort studies	Increased risk in AVR group for VTE. Similar reop rates	Low	0	0	0	0	0	0	0	0	Low	
	Late mortality	3 cohort studies	Similar b/w groups @ 5 years. No long-term data for AVS.	Low	0	0	0	0	0	0	0	0	Low	

APPENDIX B.

List of Abbreviations

AVR – aortic valve-replacing (a.k.a. aortic valve-replacing root replacement)

AVS – aortic valve-sparing (a.k.a. aortic valve-sparing root replacement)

MFS – Marfan syndrome

DCC – Data Coordination Center

INR – International normalized ratio